Executive Summary for *Arixtra*

This information is provided in response to your request for information about Arixtra® (fondaparinux sodium).

OVERVIEW

- Venous thromboembolism (VTE) is comprised of deep vein thrombosis (DVT) and/or pulmonary embolism (PE). (1)
- In the United States, the overall incidence of VTE is estimated to be as high as 117 people per 100,000 with 48 per 100,000 manifesting as deep vein thrombosis (DVT) alone and 69 per 100,000 occurring as a pulmonary embolism (PE). (2) (3)
- *Arixtra* received a Grade 1A recommendation from the American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines for Antithrombotic and Thrombolytic Therapy for VTE prophylaxis after hip fracture (including extended prophylaxis), hip replacement, and knee replacement surgeries, VTE prophylaxis in higher-risk general surgery patients who are undergoing a major procedure for cancer, and VTE treatment for acute deep vein thrombosis (DVT) or pulmonary embolism (PE). (4,5,6)
- *Arixtra* is indicated for the treatment of acute DVT, when administered in conjunction with warfarin sodium, and the treatment of acute PE, when administered in conjunction with warfarin sodium when initial therapy is administered in the hospital.(7)
- *Arixtra* is the only subcutaneously administered injectable anticoagulant that is approved for DVT prophylaxis, which may lead to PE, in patients undergoing hip fracture surgery. This indication also includes extended prophylaxis.(7,8,9,10,11) *Arixtra* is also approved for prophylaxis in patients undergoing hip replacement surgery, knee replacement surgery, and in patients undergoing abdominal surgery at risk for thromboembolic complications.(7)
- *Arixtra* offers once-daily, subcutaneous (SC), standardized dosing across all approved indications. The recommended dose for prophylaxis is 2.5 mg once daily and the recommended dose for treatment is 5 mg once daily for patients with a body weight of <50 kg, 7.5 mg once daily for body weights between 50 – 100 kg, and 10 mg once daily for body weights >100 kg.(7)

EFFICACY - PROPHYLAXIS AND TREATMENT

- Four multicenter, randomized, double-blind, parallel-group clinical studies compared the safety and efficacy of *Arixtra* to enoxaparin for prophylaxis against VTE in patients undergoing either hip fracture, hip replacement or knee replacement surgery. (12) (13) (14) (15)
- *Arixtra* 2.5 mg SC once daily was the dose evaluated in all four prophylaxis studies. The dose of enoxaparin used in two of these studies (Hip Fracture and Hip Replacement) was 30 mg SC given twice-daily and 40 mg SC once daily in the other two studies (Hip replacement and Knee Replacement). (12) (13) (14) (15)
- Results of the individual studies demonstrated that in three of the four Phase III clinical trials, *Arixtra* was associated with a statistically significant reduction in VTE (greater than 50% Relative Risk Reduction) over enoxaparin following major orthopedic surgery. (12) (14) (15)
- A double-blind, randomized, non-inferiority study evaluated the efficacy and safety of *Arixtra* versus dalteparin for the prevention of VTE in patients undergoing high-risk abdominal surgery. The incidence of VTE in the group receiving *Arixtra* was comparable with patients receiving dalteparin. (16)
- The Matisse DVT Study was a non-inferiority, randomized, double-blind clinical study that evaluated the safety and efficacy of *Arixtra* 2.5 mg, 5 mg, 7.5 mg, and 10 mg once daily compared to enoxaparin 1 mg/kg twice daily for treatment of acute, symptomatic DVT. The similarly designed Matisse PE Study evaluated the safety and efficacy of *Arixtra* 2.5 mg, 5 mg, 7.5 mg, and 10 mg once daily as compared with a continuous intravenous infusion of unfractionated heparin (UFH) for treatment of acute, symptomatic PE.(17) (18)
- Results from the two Matisse trials demonstrated that *Arixtra* is at least as effective and safe as enoxaparin for initial treatment of patients with acute, symptomatic DVT. *Arixtra* is also at least as effective and as safe as UFH for initial treatment of patients with acute, symptomatic PE.(17) (18)

SAFETY - PROPHYLAXIS AND TREATMENT

- **Prophylaxis:** In three of four orthopedic trials, *Arixtra* demonstrated similar rates of major bleeding compared to enoxaparin. A higher rate of major bleeding was seen with *Arixtra* vs. enoxaparin in the knee replacement trial, due largely to events associated with a positive Bleeding Index (BI) ≥ 2. However, when the first dose of *Arixtra* is given as recommended, 6 to 8 hours after surgery, the rate of major bleeding was 1.9% for both *Arixtra* and enoxaparin.(7) The incidence of major bleeding in the abdominal surgery trial was not significantly different between *Arixtra* (2.9%; 32 of 1112) patients when given 6 to 8 hours post-surgery and dalteparin (2.4%; 34 of 1425) patients from the first injection to 2 calendar days after the last injection.(7)
- **Treatment:** The rates of major bleeding were comparable between the *Arixtra*, enoxaparin, and UFH groups in both treatment studies.(7)

IMPORTANT SAFETY INFORMATION

- When epidural/spinal anesthesia or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low–molecular-weight heparins (LMWH), heparinoids or fondaparinux sodium are at risk of developing an epidural or spinal hematoma, which can result in long-term or permanent paralysis. The risk of these events may be higher with postoperative use of indwelling epidural catheters or concomitant use of drugs affecting hemostasis. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture. Patients should be frequently monitored for signs and symptoms of neurological impairment.(7)
- *Arixtra* is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min), patients undergoing hip fracture, hip replacement or knee replacement surgery, and abdominal surgery with body weight <50 kg (<110 lb), patients with active major bleeding, bacterial endocarditis, patients with thrombocytopenia associated with a positive *in vitro* test for antiplatelet antibody in the presence of fondaparinux sodium, or patients with hypersensitivity to fondaparinux sodium.(7)
- *Arixtra* is not intended for intramuscular administration.(7)
- *Arixtra* cannot be used interchangeably with heparin, LMWH or heparinoids, as they differ in manufacturing process, anti-Xa and anti-IIa activity, units, and dosage.(7)
- The risk of hemorrhage with *Arixtra* increases with decreasing renal function. *Arixtra* should be used with caution in patients with moderate renal impairment. Renal function should be assessed periodically in patients receiving *Arixtra* and should be discontinued immediately in patients who develop severe renal impairment.(7)

- *Arixtra*, like other anticoagulants, should be used with extreme caution in conditions with increased risk of hemorrhage.(7)
- Thrombocytopenia can occur with *Arixtra*. If the platelet count falls below 100,000/mm^3, *Arixtra* should be discontinued.(7)
- Because routine coagulation tests such as prothrombin time (PT) and activated partial thromboplastin time (aPTT) are relatively insensitive measures of *Arixtra* activity and international standards of heparin or LMWH are not calibrators to measure the anti-Factor Xa activity of *Arixtra*, if during *Arixtra* therapy unexpected changes in coagulation parameters or major bleeding occur, *Arixtra* should be discontinued. Isolated cases of elevated aPTT temporally associated with bleeding have been reported following administration of *Arixtra* (with or without concomitant administration of other anticoagulants). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.(7)
- Administration of *Arixtra* before 6 hours after surgery has been associated with an increased risk of major bleeding.(7)
- *Arixtra* should be used with caution in elderly patients.(7)

Some information contained in this response may not be included in the approved Prescribing Information. This response is not intended to offer recommendations for administering this product in a manner inconsistent with its approved labeling.
In order for GlaxoSmithKline to monitor the safety of our products, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 888-825-5249. Please consult the attached Prescribing Information.
This response was developed according to the principles of evidence-based medicine and, therefore, references may not be all-inclusive.

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